Gemcitabine (Gemzar) (2-deoxy-2,2-difluorocytidine) is a new antimetabolite being increasingly used in the treatment of solid tumors. It is an analog of deoxyctydine and cytosine arabinoside (Ara-C) (Figure 1) that has shown significant activity.

Introduction

Gemcitabine (Gemzar) (2-deoxy-2,2-difluorocytidine) is a new antimetabolite being increasingly used in the treatment of solid tumors. It is an analog of deoxyctydine and cytosine arabinoside (Ara-C) (Figure 1) that has shown significant activity as a single agent in lung, breast, pancreas, and ovarian cancers. Gemcitabine (dFdC) is activated by deoxycytidine kinase to dFdC-5′-monophosphate (dFdCMP). The latter is further metabolized to dFdC-5′-diphosphate (dFdCDP) and dFdC-5′-triphosphate (dFdCTP), which, when incorporated into deoxyribonucleic acid (DNA), results in masked chain termination (Figure 2). In comparison to Ara-C triphosphate (Ara-CTP) incorporation into DNA, dFdCTP is less readily excised from DNA by DNA exonuclease. Thus, dFdCTP accumulates intracellularly to a greater degree than Ara-CTP, which may account, at least in part, for its different spectrum of preclinical and clinical activity. In addition, dFdCDP blocks DNA synthesis by another mechanism, which is the inhibition of ribonucleotide reductase.[1]

It is now well recognized that the activity of gemcitabine is very schedule-dependent.[2] Preclinical testing demonstrated an excellent broad spectrum of antitumor activity in animals carrying human tumor xenografts.[3]

Although the initial phase I trials determined the maximum tolerated dose of gemcitabine to be 800 to 1,000 mg/m²when patients were dosed once a week for 3 of every 4 weeks, subsequent phase II trials found this dose to exhibit minimal toxicity.[4] The safety profile of gemcitabine was unusually mild for such an active agent in solid tumors. Hematologic toxicity was mild and short-lived with modest World Health Organization (WHO) grades 3 and 4 for hemoglobin (6.4% and 0.9% of patients, respectively), leukocytes (8.1% and 0.5%), neutrophils (18.7% and 5.7%), and platelets (6.4% and 0.9%). The incidence of grades 3 and 4 infection associated with this level of myelosuppression was low (0.9% and 0.2%). Transaminase elevations occurred frequently, but they were usually mild and rarely dose-limiting. Nausea and vomiting were mild, rarely dose-limiting, and generally well controlled with standard antiemetics. Flulike symptoms were experienced in a small proportion of patients but were of short duration. In cases where edema/peripheral edema were experienced, there was no evidence of any association with cardiac, hepatic, or renal failure. Hair loss was rare, with WHO grade 3 alopecia reported in 0.5% of patients. Furthermore, gemcitabine displayed minimal toxicity in elderly patients, and the side-effect profile does not seem to be affected by patient age.

Abbruzzese[5] reviewed the extensive data generated in phase I studies with gemcitabine. These studies demonstrated important schedule-dependent differences in toxicity profile and activity of gemcitabine. Frequent drug administration produced a high incidence of toxicities: in the daily schedule, flulike symptoms (fever, malaise, and headache) were experienced, and in some patients, idiosyncratic episodes of severe hypotension; in the twice-a-week schedule, the dose-limiting toxicity was thrombocytopenia. Less-frequent drug administration was better tolerated (myelosuppression was the dose-limiting toxicity), but little efficacy was observed.

The first objective of this phase I study was to determine the toxicity profile and the maximum tolerated dose of the combination of gemcitabine and UFT (uracil and tegafur in a 4:1 molar ratio) plus oral calcium folinate (Orzel) in patients with advanced cancers. The second objective was to measure the rate of objective tumor response, duration of response, and overall survival in patients treated with the combination of gemcitabine and UFT plus oral calcium folinate. The rationale for
combining gemcitabine with UFT plus oral calcium folinate is their nonoverlapping toxicities: the dose-limiting toxicity of gemcitabine is hematologic, whereas nonhematologic toxicity is the major dose-limiting toxicity of UFT plus oral calcium folinate.

**Materials and Methods**

**Eligibility Criteria**
The Human Investigational Committee approved the study at Wayne State University, and patients provided signed, written informed consent. Patients must have histologic or cytologic proof of advanced malignancy and disease evaluable for response. Life expectancy should be greater than 3 months, and patients must have a performance status of 0 to 2 on the Southwest Oncology Group scale. Serum creatinine concentration must be ≤ 1.5 mg/dL. Patients must have hemoglobin ≥ 8.0 g/dL, absolute neutrophil count ≥ 1,500/µL, platelet count ≥ 100,000/µL, and total serum bilirubin ≤ 2.0 mg/dL. Serum aspartate aminotransferase concentration must be less than 3.0 times the upper range of normal, provided patients have evidence of hepatic metastases.

**Study Design**
Dose escalations of gemcitabine and UFT plus oral calcium folinate will be according to the schema outlined in Table 1. At least three patients will be entered at each dose level until reaching the maximum tolerated dose. The 90-mg/day calcium folinate dose will be kept constant throughout the study. Dose escalations are not allowed within the same patient. A minimum of six patients will be entered at a given dose level if one or more of the initial three patients at that dose level develop 1) grades 3/4 nonhematologic toxicity (excluding alopecia), 2) grade 4 thrombocytopenia, 3) grade 4 neutropenia complicated with either fever or treatment delays of > 1 week, or 4) dose withholding during a treatment cycle (except for diarrhea).

**Drugs and Treatment**
Gemcitabine will be administered intravenously over 30 minutes on days 1, 8, and 15 of a cycle; cycles will be repeated every 28 days. UFT plus oral calcium folinate will be administered orally in three divided doses. The dose of UFT will be escalated in successive cohorts of patients, whereas the dose of calcium folinate will remain constant at 90 mg/day. The dose of UFT per day is calculated on the basis of the body surface area and rounded off to the nearest 100 mg. Immediately before a dose of UFT, 30 mg of calcium folinate will be administered orally. UFT plus oral calcium folinate will be administered on days 1 to 21 of each cycle. Treatment will be continued until disease progression or undue toxicity.

**Results**
Eight patients have been accrued to this study, five of whom were evaluable for toxicity at the time of preparing this article (Table 2). Table 3 summarizes the toxicity data. The maximum tolerated dose has not been reached, based on the follow-up of the five patients reported so far. The major toxicity is hematologic; nonhematologic toxicity has been absent at these two dose levels. One patient at dose level 1 has grade 4 thrombocytopenia but has not required any platelet transfusions. This patient was previously heavily treated with several lines of chemotherapy including alkylating agents.

**Discussion**
The combination of gemcitabine and UFT plus oral calcium folinate represents an attempt to modulate 5-fluorouracil (5-FU) pharmacodynamics in humans. Gemcitabine and UFT are both antimetabolites that inhibit DNA synthesis by at least two different mechanisms: DNA chain termination with gemcitabine and inhibition of thymidylate synthase by 5-fluoro-2′-deoxyuridylate (FdUMP). In addition, the metabolite dFdCDP inhibits ribonucleotide reductase, which is the key enzyme in the generation of deoxyribonucleotide. Gemcitabine may therefore enhance DNA synthesis inhibition by its additive effect to UFT, and also by augmenting the inhibition of thymidylate synthase and reducing the concentration of deoxuridine monophosphate (dUMP), which competes with FdUMP for thymidylate synthase.

Several studies have been initiated to determine the tolerability and the maximum tolerated dose of gemcitabine when combined with 5-FU. The combination of gemcitabine and continuous-infusion 5-FU was investigated and shown to produce neutropenia as its dose-limiting toxicity.[6] The maximum tolerated dose of the combination was gemcitabine 900 mg/m²/week (3 of 4 weeks) and 5-FU 200 mg/m²/day. In another study, the dose-limiting toxicity was nonhematologic when 5-FU 300
mg/m²/day was combined with low-dose gemcitabine (300 mg/m²/week, 3 of 4 weeks).[7] These two early reports on the combination of gemcitabine and continuous-infusion 5-FU indicated that the dose-limiting toxicities resulting from the combination, whether hematologic or nonhematologic, depended on the ratio of gemcitabine to 5-FU dose.

The combination of gemcitabine and UFT plus oral calcium folinate may be further developed in the treatment of cancers that are responsive to either drug, but particularly in disease where both drugs have shown notable antitumor activities (eg, breast cancer). The optimum schedule of administration of gemcitabine and UFT plus oral calcium folinate will also need further investigation.

References:


Links:
[1] [http://www.physicianspractice.com/review-article](http://www.physicianspractice.com/review-article)
[3] [http://www.physicianspractice.com/authors/dina-ibrahim-md](http://www.physicianspractice.com/authors/dina-ibrahim-md)
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